DEPARTMENT OF HEALTH AND HUMAN SERVICES

and

CENTERS FOR DISEASE CONTROL AND PREVENTION

convene the

ADVISORY COUNCIL FOR THE ELIMINATION OF TUBERCULOSIS MEETING

Atlanta, Georgia
October 10-11, 2001

RECORD OF THE PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

ADVISORY COUNCIL FOR THE ELIMINATION OF TUBERCULOSIS
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Minutes of the Meeting

The Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) convened a meeting of the Advisory Council for the Elimination of Tuberculosis (ACET). The proceedings were held on October 10-11, 2001 at CDC's Corporate Square Facility, Building 8, in Atlanta, Georgia. The following individuals were present to contribute to the discussion.

ACET Members
Dr. Charles Nolan, Chair
Dr. Stephanie Bailey
Dr. David Cohn
Dr. Wafaa El-Sadr
Dr. Masae Kawamura
Dr. Charles Wallace

ACET *Ex Officio* Member
Dr. Gary Roselle (VA)

ACET Liaison Representatives
Dr. Henry Blumberg (IDSA)
Ms. Fran Dumelle (ALA)
Dr. James McAuley (CCCS)
Dr. Gene Migliaccio (INS)
Ms. Carol Pozsik (NTCA)
Ms. Rachel Stricof (APIC)
Dr. Michael Tapper (SHEA)

Designated Federal Official
Dr. Ronald Valdiserri,
ACET Executive Secretary

CDC Representatives
Dr. Harold Jaffe, NCHSTP Acting Director
Dr. Kenneth Castro, DTBE Director
Dr. Rachel Albalak
Ms. Kathy Cahill (via conference call)
Ms. Viva Combs
Dr. Jack Crawford
Ms. Melody Davis
Ms. Thena Durham
Ms. Paulette Ford-Knights
Dr. Michael Iademarco
Dr. John Jereb
Mr. Jon Kaplan
Ms. Lauren Lambert
Ms. Ann Lanner
Dr. Mark Lobato
Ms. Lilia Manangan
Dr. Bereneice Madison
Dr. Scott McCombs
Mr. Scott McCoy
Dr. Scott McNabb
Dr. Bess Miller
Ms. Mary Naughton
Dr. Thomas Navin
Ms. Kathryn O'Toole
Mr. Paul Poppe
Mr. Bob Pratt
Dr. Audrey Reichard

Dr. John Ridderhof
Ms. Margie Scott-Cseh
Mr. John Seggerson
Dr. Thomas Shinnick
Mr. Jason Urbanowitz
Ms. Wanda Walton
Ms. Misty Worley
Dr. Reneé Ridzon
Dr. Elsa Villarino

Guests

Ms. Alice Alexander (TB Monitor)
Dr. Abraham Miranda (DOI)
Dr. Lisa Pascopella (California DOH)

***Opening Session*.** Dr. Charles Nolan, the ACET Chair, called the meeting to order at 8:43 a.m on October 10, 2001. He welcomed the attendees to the proceedings and opened the floor for introductions. Dr. Ronald Valdiserri, the ACET Executive Secretary, reported on administrative issues. First, all comments are a matter of public record since the meeting is open to the media and general public. Second, members with a conflict of interest on a particular issue must recuse themselves from voting or participating in the discussion. Third, the hiring freeze for all HHS Federal Advisory Committees is still in effect. Members whose terms have expired are being asked to continue to serve until the freeze has been lifted and nominees have been appointed.

Fourth, ACET's September 19, 2001 meeting with the HHS Deputy Secretary was canceled due to the events on September 11. The meeting will most likely be rescheduled after January 1, 2002. Fifth, ACET's low incidence document has been cleared by NCHSTP and other CDC centers. The draft that will be submitted to the *Morbidity and Mortality Weekly Report* (*MMWR*) for publication will be distributed to ACET within the next few weeks. Sixth, the draft statement on TB cases in the custody of Immigration and Naturalization Services (INS) was distributed by e-mail to all members. A discussion of the report is scheduled on the agenda for ACET to provide final comments before the document begins CDC's official clearance process for publication in the *MMWR*.

Update by the Acting Director of the National Center for HIV, STD and TB Prevention (NCHSTP). Dr. Harold Jaffe's status report covered the following areas. First, NCHSTP's two searches to replace Directors for the Intervention, Research and Support Branch and the Division of STD Prevention are still ongoing. Second, the House Appropriations Subcommittee passed a bill to increase the NCHSTP budget, but neither the Senate nor House has marked-up language to date. As a result, CDC is still operating at the same budget level as the previous year; the continuing resolution will expire on October 16, 2001. The bill proposes to increase funding for domestic AIDS by $53 million, global AIDS by $33 million, STDs by $9 million and TB by $9 million.

Third, one TB bill introduced to Congress amends the Public Health Service (PHS) Act to expand the Federal TB Task Force to the "Committee on Interagency Collaboration for TB Elimination." The legislation will allow broader participation by more federal agencies, non-federal members and international organizations. Another TB bill amends the Foreign Assistance Act of 1961 by declaring TB control as a major objective. Under the legislation, Congress will coordinate with the World Health Organization and other agencies to develop a comprehensive TB control program. Activities will include an expansion of directly

observed therapy (DOT) and strategies to address multi-drug resistance TB (MDR-TB). The goal of the bill is to cure at least 85% of TB cases with DOT strategies.

Fourth, the HHS Office of the Inspector General (OIG) is conducting a study on the public health impact of illegal immigrants who are paroled. Under the initiative, interagency coordination at the federal level will be reviewed to ensure that parolees with TB receive appropriate medication and do not pose a risk to communities. OIG will hold its first conference for the study at the end of October 2001.

Update by the Director of the Division of TB Elimination (DTBE). Dr. Kenneth Castro's status report covered the following areas. First, DTBE entered into cooperative agreements with state tribal agencies to address the fact that the TB rate among Native Americans is twice the national average. Under the initiative, DTBE is conducting site visits, strengthening program capacity, and participating in investigations of TB clusters in reservations. ACET members were encouraged to remain for the lunch presentation scheduled on the following day to discuss recent TB data focusing on Native Americans.

Second, the Scientific Advisory Group of Experts convened a meeting on September 11, 2001 to review the research agenda for the TB Trials Consortium (TBTC). The expert panel validated Study 26 in particular and the research agenda in general in terms of scientific and programmatic relevancy. Study 26 is being conducted at several sites to compare the efficacy of once-weekly rifapentine and isoniazid (INH) for the treatment of latent TB infection (LTBI). The expert panel recommended no changes to the research agenda.

Third, a whole-blood Interferon-γ assay was compared to the tuberculin skin test (TST) in the October 10, 2001 edition of *JAMA*. The Food and Drug Administration (FDA) will review these findings on October 12, 2001 to determine whether Interferon-γ can be licensed in the United States. A copy of the article was distributed to ACET. Fourth, along with the HHS Secretary and Mexico Minister of Health, DTBE will participate in the U.S./ Mexico binational TB meeting on October 15-16, 2001. The conference is being held for border states to improve detection and follow-up of TB-positive persons who cross either side of the border. Meeting attendees are expected to develop a binational TB card and an information exchange system. Fifth, the manuscript outlining TB morbidity data for 2000 has been cleared for publication in the *MMWR*.

Sixth, CDC's response to the Institute of Medicine (IOM) report has been revised for publication. The new version reflects comments from ACET, the National TB Controllers Association (NTCA) and other partners. The Federal TB Task Force's response to the IOM report will be published as an *MMWR Reports and Recommendations* (*R&R*). Seventh, CDC's Office of the Director and DTBE will participate in the STOP TB Partners' Forum on October 22-23, 2001. To date, Ministers of Health in 19 countries with a high TB burden have committed to attending the meeting. The goal of the forum will be to improve access to DOT strategies for diagnostic and treatment services in high-burden countries that have limited resources. Eighth, CDC, the American Thoracic Society (ATS) and the Infectious

Disease Society of America are drafting guidelines for treatment of persons with active TB. The document will be formally evaluated with focus groups to ensure all recommendations are clear and do not convey unintended messages.

***CDC's Response to the September 11, 2001 Public Health Emergency*.** Ms. Kathy Cahill, Director of the Office of Program Policy and Evaluation, conveyed that CDC mobilized into an Atlanta-based operations center to provide support to New York City and Washington, DC within hours after the events. Along with medical supplies, CDC immediately deployed a team of emergency response personnel, epidemiologists, and stockpile experts to the sites. At the request of the New York City Health Department, a second CDC team was deployed after September 11 to conduct surveillance in 15 local hospitals and among first responders.

Samples collected from the environment and workers have not shown any unusual patterns of illness to date. However, CDC will continue surveillance to detect long-term health effects. The Pentagon is conducting the majority of health-related activities in Washington, DC, but CDC has been providing support to surrounding states and cities to strengthen emergency response preparedness. This effort is also being undertaken with other state and local health departments throughout the country.

***Update on New Technology for TB Subtyping*.** Dr. Jack Crawford explained that one of CDC's major funding challenges for the upcoming fiscal year will be to secure resources to implement TB typing on a large-scale basis in the United States. CDC is focusing on this issue due to problems with current technologies. Fingerprinting is both time consuming and difficult in terms of pattern analysis and other technical aspects. The PCR-based spoligotyping method rapidly produces digital results that are easier to analyze and compare, but specificity is much lower than fingerprinting. To address these issues, mycobacterial interspersed repeat unit (MIRU) typing was recently introduced. The new technology is a form of the widely used variable number of tandem repeats (VNTR) PCR method.

MIRU typing involves a series of 50 to 100 base pairs of repetitive elements located throughout the genome of *M. tuberculosis*. Of the available pairs, 12 are considered to provide maximum variability among strains and be useful for VNTR typing. The method to analyze MIRU typing involves PCR amplification and a series of primers located in regions flanking the repetitive elements. MIRU repetitive elements can also be examined with a DNA sequencer. The advantage of this method is an automated and exact confirmation of size within one or two base pairs. Four dyes are read when MIRU typing is used with an automated sequencer on a large scale basis for high throughput. While one dye is used for molecular standards, the remaining three can be used to label PCR products. Because PCR products run at discreet sizes, the amplification can be designed to provide overlapping ladders.

In the future, CDC hopes to add four different PCR products per dye to run all 12 samples in a single lane. The MIRU analysis can now be run for 96 TB strains in 12 hours once the

PCR products have been completed. VNTR is a practical technology, but its ability to perform as a typing tool and the type of information generated are uncertain. In an effort to answer these questions, a study was conducted in which 70 *M. tb* isolates were selected to analyze different typing methods in terms of specificity and ability to reproduce. The results showed 69 fingerprint, 47 spoligo and 60 MIRU patterns. These findings suggest that the specificity of MIRU typing is higher than spoligotyping, but lower than fingerprinting.

In another study, CDC obtained 180 isolates to further test MIRU typing. All isolates had low fingerprint copy numbers and were problematic in terms of specificity. Of the total number of isolates, seven showed consistent results among MIRU, spoligo and fingerprint patterns. The allelic diversity confirmed that the amount of information generated varied among the different repetitive elements. CDC determined that all 12 MIRU repetitive elements should be analyzed because additional data are obtained when complete sets are used. These findings indicate that MIRU typing is a useful technique in subdividing strains, but spoligotyping and fingerprinting are both needed to obtain the best subdivisions. CDC is considering a simple order in which to use the three technologies: spoligotyping to select unique strains; MIRU typing to detect clustered isolates; and fingerprinting to subdivide clustered isolates where possible. CDC is currently applying MIRU typing in six low-incidence states: Colorado, New Hampshire, Montana, Vermont, West Virginia and Wisconsin.

Based on an analysis of findings from four studies, CDC identified both advantages and disadvantages. On the one hand, MIRU typing is a rapid PCR-based method that can be run on low-density cultures. The technology is very well suited for automated analysis; digital results would be easy to analyze and compare. On the other hand, MIRU typing is more difficult to run than spoligotyping. A substantial investment of approximately $100,000 would be required up-front because an automated sequencer would be needed. Isolates would need to be sent to regional laboratories as well. Although MIRU typing appears to be promising as a first-line screening tool, CDC does not believe the technology can be easily implemented in state health department laboratories at the present time. Spoligotyping is currently the best method for local laboratories. Fingerprinting and MIRU typing could be conducted by regional or specialized laboratories on an as-needed basis.

ACET was surprised by CDC's recommendation for local laboratories to use spoligotyping since fingerprinting is considered to be the gold standard. CDC clarified that fingerprinting is not ideal in terms of complexity, cost and time. Spoligotyping should first be used as a rapid screening tool to detect unique strains. This technology can produce accurate results in 24 hours with a positive BACTEC culture; the cost is $20 per kit. The more costly, difficult and time-consuming methods of MIRU typing and fingerprinting should then be applied to questionable isolates. MIRU typing can generate results within the same time frame as spoligotyping, but transit time from the state laboratory would need to be taken into consideration. The cost is $20 per test; however, instrumentation and laboratory personnel with more expertise and skills to operate the sequencer are additional expenses.

Fingerprinting would require at least two weeks to grow cultures and then an additional week to complete the process. The cost is $50 per analysis. ACET informed CDC that many laboratories will have questions about using MIRU typing for TB control and prevention at the local level. The linkage between the laboratory and epidemiologic components of the technology should be communicated as well. CDC confirmed that a manual will be developed to describe the basic molecular biology of MIRU typing. Additionally, TB controllers and laboratory specialists hold face-to-face conferences to gain a better understanding of new technologies.

***Update on Regional TB Laboratory Services*.** Dr. Thomas Shinnick mentioned that cooperative agreements to upgrade and facilitate improvements in TB laboratory performance have been in existence since 1992. CDC provides personnel, equipment and supplies under this $10 million initiative, but funding has remained level since 1995. The cooperative agreements have been extremely beneficial since most laboratories now meet CDC's recommended turnaround time; however, challenges still exist. As the number of samples submitted to laboratories for testing decreases, maintaining proficiency and personnel with skills to use technologies becomes more difficult. To address this issue, a number of actions can be taken. Proficiency testing training programs can be offered to workers more frequently. Low-volume laboratories can contract difficult tests to high-volume facilities. Laboratories can collaboratively increase the number of specimens by combining coverage areas. CDC encourages laboratory partnerships and will assist in this effort.

Despite the solutions to maintain proficiency, the most significant challenge will be to incorporate more expensive molecular tests in laboratories with level funding. New York's voluntary FastTrak System serves as a model to address this issue. Local laboratories process specimens, perform AFB smear microscopy and immediately report results to physicians. If smear-positive samples are from new patients, specimens are shipped to the state laboratory for testing, culture methods and nucleic acid amplification (NAA) tests. The state laboratory provides these services in a rapid and cost-efficient manner. The New York model has the potential to be replicated at the national level.

For example, 10,000-15,000 first-time smear-positive specimens are likely to be seen in the United States. Five or six national FastTrak laboratories would be placed in Atlanta, Chicago, Dallas and other transportation hubs throughout the country. State laboratories would have the same responsibilities as local laboratories in the New York system, but national FastTrak laboratories could provide additional services, *i.e.*, genetic tests for drug resistance, first- or second-line drug susceptibility testing, rapid culture confirmation and strain typing. The California state laboratory serves as a model for providing rapid culture confirmation. Local laboratories process specimens, perform AFB smears and inoculate BACTEC vials. The vials are then shipped to the state laboratory for identification, drug susceptibility or further testing. The services are targeted to low-incidence areas within the state.

Several benefits can be gained by building on the California and New York models to develop a national system. The cost per test would decrease; less equipment would need to be purchased; and testing could be conducted seven days a week in a cost-effective manner. Moreover, the national system may allow state laboratories to have access to strains normally processed by private laboratories. The disadvantages of a national system include logistical issues and costs to transport samples to the nearest FastTrak laboratory. Moreover, communication in reporting results may be delayed and rapport between the TB control program and laboratory may be lost.

CDC believes the advantages would outweigh the disadvantages if the national system is appropriately developed with strong lines of communication. Funding from the cooperative agreements would support NAA, personnel and other needs of the FastTrak laboratories; states would be responsible for transportation costs. However, a full-service national reference laboratory would not be established at the outset. In the short term, NAA would be provided to low-incidence areas that do not have the resources or infrastructure to perform the test. In the long term, rapid culture and identification would be facilitated by national FastTrak laboratories. CDC estimates that $500,000 to $1 million will be needed to launch the national system. Since level funding is projected for the cooperative agreements through 2002, no action can be taken before 2003.

ACET agreed that the national system would be beneficial for low-incidence areas, but significant changes would need to be made for implementation in high-incidence areas, *i.e*., laboratory reorganization, stronger communication, a rapid method of transportation, faster turnaround times, and enhanced use of the Internet and other electronic media. In the interim of developing the national system, CDC was asked to more closely collaborate with private laboratories to improve the quality of results and decrease turnaround times to state laboratories. Agreement was reached to discuss TB laboratory issues in more detail at the next ACET meeting; an update on microbacteriology laboratories would be included. Appropriate representatives to present the public health laboratory perspective would be present as well.

***Update on TST*.** Dr. Elsa Villarino explained that TST has been widely used to screen for LTBI since the 1930s. The two commercially available tuberculin reagents are standardized with purified protein derivative-S (PPD-S), which is stored and released for use by the FDA. However, the antigenic structures and precipitation methods of the commercial reagents differ. Aplisol is isolated by ammonium sulfate, while Tubersol is isolated by trichloroacetic acid. CDC reviewed the available literature about the rate of false positives with commercial reagents, but several flaws were noted with the data: small and high-risk study populations; retests for false positives only; reading differentials; host variability of up to 65 mm in 95% of subjects; and omission of denominator data and TST lots.

To address these issues, CDC conducted a study to compare the specificity of the two reagents with PPD-S. The double-blind trial was implemented at six study sites among 1,555 low-risk persons ages 18 to 50 years. Study participants were born in Canada or the

United States and had no history of BCG or exposure to *M. tuberculosis*. Along with two lots of both Aplisol and Tubersol, two injections of PPD-S1 was used on 25% of the sample; PPD-S1 and PPD-S2 were used on 75% of the sample. The study was powered to detect a 2% difference in false positive rates. Two trained observers blinded to each other interpreted the TST results. No significant variability was found among readers, PPD lots, hosts or sites with low or high prevalence of non-TB mycobateria.

The study showed the following results. The specificity of both Aplisol and Tubersol was equally high and similar to PPD-S. Reactions produced were larger with Aplisol and smaller with Tubersol when compared to PPD-S, but these differences did not affect TST interpretations. Both Aplisol and Tubersol correctly classified a comparable number of persons not infected with TB. Although Tubersol is less suited as a screening test, either product can be used with confidence for TST, particularly in low-incidence areas with high rates of false-positives. The sensitivity and specificity of TSTs are unknown and imperfect because no test can formally prove that LTBI is present or absent. Indeed, hypersensitivity reactions, inadequate reliability, false-positive TST results and other problems with both Aplisol and Tubersol have been reported to DTBE and the published literature. CDC recommends that erythema and bruising be disregarded as positive reactions.

The Mantoux TST is still the most accurate method to diagnose LTBI. This product requires that a targeted high-risk population be tested; a dose of a well standardized tuberculin preparation be properly administered; and personnel be trained to correctly interpret any observed reaction. CDC realizes that the percentage of positive skin test results can increase after tuberculin preparations are changed. To address this issue, available data should be reviewed to estimate the likelihood of disease. The potential benefits and risks of proposed interventions following a true reaction should be assessed, such as x-rays or sputum tests. Additional information should be gathered or a repeat test should be performed.

ACET did not agree with the conclusion that Aplisol and Tubersol equally perform as TST products. CDC's data showed a 1% difference in specificity among a low-risk population. For facilities that perform a large number of tests each year, the 1% difference could become a high rate of false positives. Despite CDC's finding of "no significant variability among PPD lots," this problem has been noted by TB controllers, nurses and other field personnel for several years. A suggestion was made for CDC to recommend retesting when a false positive result is suspected based on an individual's history.

The possibility was raised of ACET outlining problems with Aplisol and Tubersol in an evidence-based statement in the *MMWR*. A thorough evaluation of conversions, reported outbreaks and other epidemiologic components could be included in the recommendation. Data could be reviewed to determine if Quanti-FERON can be recommended as an alternative to available commercial reagents.

***Update on the Strategic Plan for TB Training and Education*.** Mr. John Seggerson conveyed that development of the strategic plan began in 1998 with six workgroups. More

than 160 members represented the private sector, correctional facilities, high-risk institutions, the public health sector, foreign-born patients in the United States, and international TB and health care. All six workgroups developed position papers that were consistent with the purposes of the strategic plan: promote collaboration between U.S. and global organizations; promote awareness among organizations supporting high-risk groups; promote training efforts among providers in high-risk communities; and identify available training, education and resources.

Several actions were taken during a strategic plan summit held with workgroup members: position papers were reviewed; consensus was reached on the strategic plan mission; needs and priorities of TB training and education were identified; strategic plan objectives, roles and responsibilities were defined; and an Implementation Committee (IC) was established. The members agreed that the strategic plan should "promote and guide training and educational efforts to control and eliminate TB." IC has met on a regular basis since 1998 to review, monitor and modify the strategic plan objectives. Several ACET members participate in this initiative.

The majority of the short-term objectives are being met, but CDC is particularly pleased that awareness has increased about TB issues and the need for training. Other benefits of the strategic planning process include the TB Training and Education Network, a resource inventory, dissemination of materials, extensive outreach and research, and an expansion of international TB activities. IC recently met to evaluate progress, discuss future plans, and design a complimentary mechanism for the strategic planning process and new training initiatives. The need for ACET's support was strongly emphasized, particularly since funding for the strategic planning process will end in December 2001. Support for the initiative was originally provided by CDC through the Model Centers.

Despite budget constraints, IC decided not to disband to ensure that momentum for TB training and education continues. For the remainder of the year, IC will undertake several activities: strengthen partnerships with TB training and education stakeholders; secure new funding, support and collaborators; better utilize existing resources; review the original position papers to identify outstanding objectives; and publish an updated version of the strategic plan. The Curry Center has requested $150,000 from CDC to support the basic strategic planning process for one year, but additional funding will be needed for specific projects and logistical costs of meetings.

ACET agreed that education and training are critical for providers, decision-makers and patients, particularly as TB incidence continues to decrease. As a next step in the strategic planning process, culturally and linguistically appropriate TB education materials should be developed and disseminated to foreign-born patients. The majority of ACET's discussion focused on the funding shortage. The strategic plan was designed as a desktop report, but the document should be more widely distributed to demonstrate progress in TB education and training since 1998. Outstanding needs and priorities should be identified as well.

Concrete models of the strategic plan actually being used and making an impact should be showcased. Other federal agencies should be aggressively marketed for resources and support in implementing the strategic plan. For example, TB education could be incorporated into existing patient education materials and activities by INS and the Veteran's Administration. Additional resources may also be provided if the strategic plan is framed in the context of the IOM TB elimination report. ACET formally endorsed the strategic planning process and strongly emphasized the need for CDC to secure funding to continue the project beyond December 2001.

***Epidemiology of TB in the Southeastern United States*.** Ms. Lilia Manangan reported that CDC collected data from nine southeastern states with 1999 and 2000 case rates above the national average of 5.8/100,000. To examine and compare TB trends, states were divided into three categories. Group 1 is seven southeastern (SE-7) states: Alabama, Arkansas, Georgia, Louisiana, Mississippi, South Carolina and Tennessee. Group 2 is Florida and Texas (F&T), while Group 3 is all other states (AOS). CDC decided to separate F&T from other southeastern states due to the large morbidity in these areas.

In 2000, SE-7 represented 11% of the total U.S. population and 15% of all TB cases in the country. F&T had 37 million residents and more than 2,500 TB cases in the same year. Case rates for both SE-7 and F&T were higher than the combined rate for AOS from 1990-2000. However, case rates for all three groups substantially declined to half the 1990 rate and are similar to national trends. CDC's data were also broken down to show case rates by race/ethnicity. Blacks accounted for more than one-half of cases in SE-7, one-third in F&T, and one-quarter in AOS. Whites accounted for one-third of cases in SE-7 and one-quarter in both F&T and AOS. Hispanics accounted for less than 10% of cases in SE-7, one-third in F&T and one-quarter in AOS. Asians accounted for less than 10% of cases in both SE-7 and F&T and one-quarter in AOS.

Overall in SE-7, at least 95% of TB cases occurred among blacks and whites, but blacks accounted for more than 50% of cases. Of the three groups, SE-7 had the largest proportion of U.S.-born residents, while AOS had the smallest. Blacks and whites ages 25-64 years accounted for the largest proportion of cases in all three state groups. While TB case rates declined among U.S.-born persons from 1990-2000, the proportion of cases increased among foreign-born persons in all three state groups. Mexico, Vietnam, India, Haiti and the Philippines were the largest contributing countries. From 1993-1999, the rate of HIV co-infection among TB patients was less than 10% in SE-7, but the co-infection rate in Florida alone was twice the rate in AOS. Overall, SE-7 had low and relatively stable rates of HIV co-infection.

For clinical characteristics, 80% of cases in all three groups were culture confirmed. INH resistance was highest in AOS and lowest in SE-7; the MDR rate was the same among all groups. F&T and AOS treated with the initial four-drug regimen at a higher rate than SE-7. The use of DOT was higher in SE-7 and F&T than AOS. The percentage of patients who completed therapy in one year or less was 75%-80% among all groups. For all three groups, diagnostic evaluation and treatment were provided by health departments at a rate

of 30%-50%. Compared to all three state groups, SE-7 had the lowest percentage of care by private providers.

Since the data represent a preliminary analysis, CDC requested ACET's assistance in identifying other areas where information should be gathered. Due to time constraints, data were not presented on TB case rates of rural verus urban populations; TB resources spent in southeastern states versus other areas; or the Cantwell study. NCHSTP confirmed that this information would be sent to ACET.

In response to CDC's request, ACET listed additional areas where data should be collected for southeastern states: epidemiologic profiles at the local level; percentages of diagnosis delays; rates of reactivation versus new infection; numbers of contacts solicited and identified; differences in program performance; use of RFLP; and numbers of preventable cases. By combining F&T, however, CDC may be missing opportunities to collect additional data or conduct interventions among sub-populations because the epidemiology of TB is different in both states.

ACET engaged in an extensive discussion about the significant TB disparity among U.S.-born blacks in SE-7. Since the majority of TB personnel are not black, racial, cultural and social issues may not be identified as barriers to completion of therapy in this population, *i.e.*, mental health problems, substance abuse, homelessness, poverty, lack of access to care and lack of trust. As a result, U.S.-born blacks are regarded as foreign-born persons whose treatment has historically been denied or neglected. Until new and innovative strategies are developed, the TB disparity among blacks will continue. ACET generally agreed not to focus on published studies that suggest blacks are genetically predisposed to TB. Emphasis would only be placed on social, racial or cultural factors for which interventions, actions or recommendations can be made.

To actually achieve the TB elimination goal in the United States, ACET noted that the high case rates in southeastern states can no longer be ignored. For example, CDC's data showed that case rates declined in SE-7 and F&T from 1990-2000, but the case rate in Georgia has steadily increased since 1998. The HIV co-infection rate is high in Atlanta as well. In addition to race/ethnicity, socioeconomic status plays a significant role in TB disparities as well. TB became an eligible disease for Medicaid reimbursement in 1993, but only nine states in the entire country have acted on this opportunity. As a result, TB is particularly distressing among poor populations.

Moreover, political will is low because very few southeastern states prioritize TB. This critical issue is a concrete example of the need for health departments to strengthen partnerships with non-governmental, community-based, social and advocacy organizations. Most notably, the Congressional Black Caucus is on record with its strong interest in reducing racial health disparities. ACET made two suggestions as an initial effort to address this issue. First, undertake a project to examine the molecular epidemiology of TB in the southeast. Second, compile CDC's data into an *MMWR* article to present to policymakers and community leaders. ACET did not want to table this critically important

topic until its next meeting. To ensure that actions were immediately taken, agreement was reached to form a "TB in Southeastern States Workgroup" with an emphasis on disease risks among blacks. ACET would identify workgroup members on the following day.

Update on Response to Liver Injury Associated with Rifampin/Pyrazinamide (RZ) Treatment of LTBI. Dr. Michael Iademarco reviewed the time-line of major activities associated with liver injury reports. In October 1998, the HIV guidelines were published as an *MMWR R&R*. The 2RZ regimen was recommended for use in HIV populations. From June-October 2000, targeted testing and treatment guidelines for LTBI were published. DTBE received the first report of an adverse event from RZ. Liver injury reports were presented to ACET; two cases were described in the *MMWR*; preliminary data were presented at the ATS conference; revised recommendations were drafted at the NTCA meeting; modified guidelines were published in the *MMWR*; and reprints were published in *JAMA* and the *American Journal of Respiratory Critical Care Medicine*.

During this time, DTBE met on a regular basis to address scientific and management issues related to the adverse events. The group defined severe liver injury associated with RZ treatment of LTBI as "admission to a hospital or fatal outcome." From October 2000-October 8, 2001, 83 cases were reported to DTBE. Of the 56 cases from 21 jurisdictions that did not meet the case definition, 38 included RZ, 18 were investigated and four were fatalities. Of the 27 severe cases from 11 jurisdictions, 20 were investigated and six were fatalities. The characteristics of the 27 severe cases were a median age of 46 years, 17 males, 13 Hispanics, eight blacks, four Asian/Pacific Islanders and two whites.

The cases led to the revised guidelines that were published in the *MMWR* in August 2001. The major changes were a stronger distinction between HIV-infected and HIV-uninfected persons, more emphasis on patient selection, and an additional focus on clinical and biochemical monitoring. DTBE is currently in the process of incorporating the revised guidelines into the modified PHS rating system (PHSRS), core curricula and other publications. The strength of PHSRS recommendations is scored as "A" for preferred, "B" for alternative, and "C" for consideration if A and B are not viable options. The quality of evidence to support PHSRS recommendations is scored as "I" for a randomized clinical trial; "II" as a clinical trial or randomized clinical trial derived from a different population; and "III" as expert opinion.

The current recommendations for 2RZ among HIV-negative and -positive persons are B(II) and A(I), respectively. DTBE's revised recommendations for 2RZ among HIV-negative and -positive persons would be C(II) and B(I), respectively. The change is supported by the fact that none of the reports of hepatotoxicity occurred among HIV-positive persons. As a result, clinical trial data would not translate into practice. Overall, the nine-month INH regimen is still preferred, while 2RZ and four months of daily rifampin are alternate regimens. DTBE is transferring the liver injury activities from the Field Services Branch to the Surveillance and Epidemiology Branch. Investigations will continue and a retrospective multiple cohort will be followed to determine risk factors and rates.

ACET reinforced the need for DTBE to convey strong messages and disseminate materials clearly stating that the revised guidelines only apply to the treatment of LTBI and not disease. Another recommendation that could potentially be misinterpreted is the C(II) rating for 2RZ among HIV-negative persons. The message implies that the regimen should not be used. With respect to PHSRS in general, ACET pointed out that issuing guidelines by letters and Roman numerals is vague and will be confusing to field personnel. Since PHSRS is a standardized system, DTBE was advised to always include a legend to clearly define recommendations that are disseminated. DTBE agreed to postpone publishing the revised C(II) rating until stronger supporting evidence is gathered. ACET was pleased with DTBE's plans to follow a retrospective multiple cohort and place more emphasis on clinical and biochemical monitoring. These efforts will assist in collecting denominator data. ACET requested that additional information gathered by DTBE be presented at a future meeting.

There being no further discussion, Dr. Nolan recessed the ACET meeting at 5:06 p.m. on October 10, 2001.

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***Update on Managed Care and TB Laboratory Services*.** Dr. Nolan reconvened the ACET meeting at 8:40 a.m. on October 11, 2001 and yielded the floor to the first presenter. Dr. Lisa Pascopella, of the California Department of Health Services, conveyed that a study was conducted by the state in 1998 to determine whether changes in health care delivery systems impacted TB laboratory services. Study participants were evaluated in two areas based on published guidelines by CDC and the Association of State and Territorial Health Officers. "Recommended methods for TB testing" included fluorochrome stains for smear microscopy and AFB, liquid culture for growth, rapid methods for identification, and drug susceptibility testing. "Timeliness of reporting" included AFB smear results within 24 hours of collection, TB complex identification within 21 days of specimen receipt, and primary drug susceptibility test results within 30 days of specimen receipt.

In addition to determining recommended methods for TB testing and timeliness of reporting, a third objective of the study was to identify the proportion of TB patients whose TB testing was paid for through a managed care health delivery system in California. Unlike similar studies that only analyzed laboratories, the California investigation examined patients as well. The study population included 300 *M. tuberculosis* culture-positive patients from four large jurisdictions in the state: Los Angeles, Riverside, San Francisco and Santa Clara. These areas accounted for 47% of TB cases in California in 1998. Data were gathered from TB control programs, a qualitative survey of laboratory practices, public health laboratories and records from other laboratories.

Of the 55 laboratories that served the patient population, 54 participated in the study. Of those, 63% were hospital laboratories; 13% were public health laboratories; 20% were independent, private or commercial laboratories not associated with a particular health maintenance organization (HMO); and 4% were HMO laboratories associated with Kaiser or another staff model HMO system. Of the 300 TB patients in the study, 23% were

insured by a managed care health plan, 53% were insured by a non-managed care system, and almost 25% could not be categorized.

The data were encouraging in terms of the recommended methods used. From the patient perspective, the fluorochrome method was used at a rate of 91%, liquid culture was used at a rate of 94%, rapid methods for identification were used at a rate of 100%, and rapid methods for drug susceptibility testing were used at a rate of 88%. From the laboratory perspective, 80% used the fluorochrome method, 86% used liquid culture, 100% used rapid methods for identification, and 84% used rapid methods for drug susceptibility. Despite the solid numbers, however, California identified areas where patient care and treatment could be improved. Of the study participants, 30% of hospital laboratories needed to increase use of fluorochrome for AFB smear microscopy, while 25% of private laboratories needed to use rapid methods for drug susceptibility testing.

For timeliness of reporting, 135 AFB smear positive specimens were obtained from the 300 participating patients. Of those, 78.5% were reported within one day from receipt in the laboratory. Turnaround times are critically important in terms of TB control. The data showed that 94% of patients began treatment within seven days if AFB results were reported one day after receipt, but this figure decreased to 80% if the AFB report was delayed longer than 24 hours. Reporting times among independent non-HMO, public health and HMO laboratories were found to be lower than hospital laboratories. The data also showed that public health and independent non-HMO laboratories are most affected by transportation delays between specimen collection and receipt.

Laboratory performance was weaker for culture-positive specimens. The data showed that 47% of laboratories reported within 21 days from collection, while 56% reported within 21 days from receipt. The delayed turnaround times were attributed to AFB smear microscopy and identification tests being conducted in different laboratories. Compared to HMO and hospital laboratories, public health and private laboratories transported specimens to referral laboratories more often.

Dr. John Ridderhof mentioned that similar to the state study in California, CDC conducted a national study of laboratory practices. In terms of recommended methods for TB testing, most of the 2,544 laboratories that perform mycobacteriology are based in hospitals. Of the 1,940 laboratories that participated in a CAP survey, 71% used the fluorochrome method. In a sample of 155 laboratories from the CLIA database, 85% used a liquid culture system. Based on a national survey of susceptibility testing, most laboratories used the recommended BACTEC system. The survey also found that 69% of primary drug susceptibility testing is conducted by public health laboratories.

With respect to turnaround times, 80% of the 43 state laboratories received specimens after 24 hours. As in California, the need to transport specimens to referral laboratories was found to be a major source of delay at the national level. Despite the fact that many full-service laboratories are proficient in new technologies, rapid smears for treatment decisions cannot be provided. In many cases, mycobacteriology still requires referral

laboratories and different levels of service. These findings reinforce the need for public and private laboratories to strengthen coordination, particularly as TB cases decrease. However, algorithms and referral methods currently being used are too complex for one specific solution.

CDC found that the most effective mechanisms to resolve these problems are those developed at the local level: the FastTrak system used in Florida and New York; inoculation and referral of liquid media cultures to a full-service laboratory in California, New Mexico and Utah; and promotion of rapid methods and coordinated services between public health and private laboratories in Minnesota, Washington State and Wisconsin. CDC has implemented state-based demonstration projects of a National Laboratory System (NLS) in Michigan, Minnesota, Nebraska and Washington State. The NLS initiative is a partnership among laboratories at federal, state and local levels as well as independent laboratories in hospitals and physician office laboratories. An assessment is initially made of laboratory services and then collaborative efforts are made to change or improve practices.

ACET indicated that perhaps a legal requirement could be established for all TB isolates to be sent to public health or state laboratories. A suggestion was made for ACET to form a workgroup with the following charges: update recommendations for TB laboratory services; suggest areas where additional research and demonstration projects are needed; determine the costs of states that serve as reference laboratories; and identify appropriate representatives from CDC, NTCA and the Association of Public Health Laboratories (APHL) to assist in this effort. Since two workgroups had already been formed during the meeting, ACET decided to revisit this issue during the discussion of its business.

***Update on Treatment of TB Cases in INS Custody*.** Dr. Masae Kawamura reminded ACET of the Chair's charge to the INS Workgroup at the previous meeting. First, an *MMWR* article would be drafted based on data in the workgroup report and DTBE's statement on the treatment of persons in custody with active TB. Second, the report would be forwarded to CDC's Office of General Counsel (OGC) to ensure the proposed legislative options are legally appropriate. Third, the report would be presented during the Chair's meeting with the HHS Deputy Secretary. The purpose of this discussion would be to encourage the establishment of a federal workgroup among INS, the Department of Justice (DOJ) and the Division of Global Immigration and Quarantine.

The draft workgroup report being proposed for publication in the *MMWR* covers the following areas: background and data among INS detainees with TB; barriers to care of TB patients in INS facilities; impacts of current administrative policies and procedures; summaries of actual cases and data; and the following ACET recommendations. First, current mandatory deportation policies should be changed or amended to make exception for TB due to international public health threats of incomplete treatment. For example, a humanitarian release could be implemented among non-felons or detainees could be paroled until treatment is completed within guidelines of state health and safety laws.
Second, collaborative mechanisms could be developed between INS and TB programs to ensure effective communication and notification when a patient is diagnosed, released or

transferred. Third, the medical hold authority of the Division of Immigration Health Services (DIHS) could be expanded beyond current guidelines. DIHS currently recommends to INS that TB patients be isolated until smear-negative. Fourth, a policy could be enacted that allows deportation only if the receiving country will accept the patient and provide treatment to complete TB therapy. The domestic TB controller would need to review and approve the treatment plan before deportation. Fifth, a policy could be enacted that requires reporting of suspects in INS custody to DIHS health officers as well as state and local TB programs in the receiving jurisdiction.

Sixth, facilities willing to accept and treat difficult TB cases in INS custody could be identified. Standardized TB care would need to be agreed upon and established with guidelines to consult TB experts for complex or drug-resistant cases. The next steps in this effort will be for both ACET and OGC to provide feedback on the report in general and the six recommendations in particular. Additionally, ACET should discuss its role in OIG's investigation of undocumented persons with TB who are paroled into communities. ACET should also consider whether broader input from other border programs will be needed before the report is published in the *MMWR*.

Mr. Jason Urbanowitz of OGC pointed out that ACET's most significant legal obstacle will be expanding the medical hold authority of DIHS. Because the language can be viewed as a deprivation of an individual's basic fundamental liberty, the recommendation would be held to the highest Constitutional standard. A less restrictive recommendation, such as the use of DOT, is more likely to pass Constitutional scrutiny. For persons who are considered public health threats, the language would need to be interpreted on a case-by-case basis. **ACET's** deliberations on the report are outlined below.

- Structure the language as broad recommendations to reflect ACET's role as an advisory body. For example, "ACET recommends that HHS determine the feasibility of or explore options to achieve ..."
- Clarify recommendation 3 in an effort to overcome the legal obstacle. For example, request that the medical hold authority be expanded just to transfer patients to a facility for treatment and completion of therapy. Place more emphasis on the public health threat of TB patients who have not completed treatment being released into communities.
- Incorporate stronger language or recommend a uniform policy to emphasize the role of contract jails for standardized TB care and reporting. For example, "screening and reporting of TB cases should be conducted consistent with local public health laws and regulations." Partner with the Jail Standards Commission in this effort by requesting that sanctions be enforced for non-compliance.
- Engage DOJ as an active partner because federal deportation judges have authority to deport persons regardless of health status.
- Collaborate more closely with TB-NET because data gathered by this organization can support the recommendations. For example, the workgroup

report does not mention TB-NET's recent investigation in which TB patients were tracked upon entering the system.

- Discuss the workgroup report during the upcoming U.S./Mexico binational TB meeting since the HHS Secretary and Mexico Minister of Health will be in attendance. The discussion should focus on recommendation 4 which states that the receiving country will need to accept the patient and provide treatment to complete TB therapy.
- Incorporate language to convey that reporting of INS detainees would be "expected" since reporting of persons under federal jurisdiction may not be required.

Because ACET is already on record with its recommendation to parole persons in INS custody with active TB, Dr. Kawamura suggested that the draft workgroup report be presented during OIG's upcoming entrance interview at CDC. However, Dr. Valdiserri clarified that the document should not be shared with OIG at this time. ACET is not operating under a quorum; therefore, a formal vote cannot be taken to approve the current version of the document. CDC will convey to OIG that ACET has a strong interest in TB cases in INS custody and is currently drafting recommendations for publication in the *MMWR*. Dr. Valdiserri realized that the document will need to be thoroughly reviewed to resolve outstanding policy and legal issues. Additional comments should be provided in writing to Dr. Mark Lobato within the next week. The revised version will be circulated to all ACET members by mail before the next meeting. The original INS Workgroup will be reconvened to finalize the draft.

***Update on Health Care Worker (HCW) Guidelines*.** Dr. Reneé Ridzon remarked that the TB infection control guidelines are being revised because the language was found to be outdated and confusing to many duty officers. Along with hospitals, the updated recommendations now address outpatient facilities, TB clinics, outreach workers, laboratories and EMS services. New sections include "frequently asked questions," a web-based assessment tool, additional details on engineering controls, and information sources, *i.e.*, Internet addresses and document names. The format of the guidelines is being changed as well. Recommendations are now outlined in the body of the document, while details are described in supplements. Updated information in the supplements will discuss 2RZ, laboratory data and the new treatment guidelines.

Risk assessment guidelines will be facility-wide and more simple. A new risk classification system for TST frequency is being proposed in which persons who need to be tested will be limited to those with exposure or potential exposure to patients with TB. Facilities will be classified as low, medium or high risk; the size of the facility has been taken into consideration as well. Low risk would be three or less patients per year and fewer than 100 beds in small or outpatient facilities, and four to six patients per year and 100 or more beds in large facilities. Medium risk would be the same bed sizes as low risk, but above the patient limits. High risk would be facilities with evidence of ongoing transmission. Data show that 25% of U.S. hospitals have 100 beds or less.

CDC is proposing that TST be performed on all persons at baseline in all three types of facilities, but follow-up would differ. Follow-up TST would be conducted in low-risk facilities only among exposed persons. Annual TST would be conducted in medium-risk facilities among persons with potential and actual exposure. TST would be conducted in high-risk facilities every three months until the problem is under control. With respect to engineering controls, more clarity has been provided on ventilation and pressure. Based on recommendations from the American Institute of Architects, the revised guidelines now refer to a negative pressure room as an "airborne infection isolation room" (AIIR). The new term applies to different settings, including laboratories and rooms to place patients with suspected TB.

The pressure differential from the hallway to AIIRs has increased to 0.01 inch from 0.001 inch for better monitoring and maintenance of air flow leaks. AIIRs should be monitored prior to occupancy, daily when occupied by an isolated patient, and monthly when not in use. AIIRs in laboratories should be monitored daily. Existing AIIRs should undergo six or more air changes per hour and 12 or more when feasible, but new AIIRs should undergo 12 or more. Of those, two should be outdoor air. The revised TB infection control guidelines also discuss HEPA filtration and UVGI. For the respiratory protection program, a medical screening form for HCWs will be included in the document. Annual fit testing will be recommended in the revised guidelines, but efforts are currently being made for respirators to fit different facial sizes and provide protection at a threshold of 20. More emphasis is being placed on design and manufacturing, while less focus is being given to individual fit.

ACET recommended that the proposed system be clearly defined as a "facility risk classification" to avoid being misinterpreted as an individual risk. ACET pointed out that changes to the respiratory protection program follow ANSI standards rather than rules by the Occupational Safety and Health Administration (OSHA). The new recommendation will be extremely problematic and costly for programs because annual fit testing of N95 respirators for TB is not required by OSHA. Since fit testing is the most contentious area of the revised guidelines, CDC proposed that ACET members attend the meeting scheduled in January 2002 to further discuss this issue. The possibility was raised of ACET issuing a formal statement on fit testing to the National Institute of Occupational Safety and Health.

Status of TB Epidemiology Studies Consortium (TBESC). Dr. Scott McNabb conveyed that since the previous update on this activity, 21 contracts have been signed with health departments, universities and non-governmental organizations. Of the 22 TBESC members, 14 have been fully funded for task 1. Under the contract, CDC must have provided a minimum of $50,000 to all TBESC members after ten years. Both TBESC and TBTC operate under an empowered environment and peer-reviewed monitoring to build capacity, but the missions and memberships of the two activities differ.
While TBTC conducts clinical trials with academic institutions only, TBESC performs epidemiologic, behavioral, economic, laboratory and operational research through formal partnerships with academic institutions and health departments at state and big-city levels. CDC has hired a senior epidemiologist and program manager for TBESC to begin establishing communication. TBESC members will soon be asked to submit quotes for

tasks 3 and 4. During the first TBESC meeting in December 2001, members will begin developing bylaws, a national TB research agenda, and standard operating procedures for research, specimens and data. CDC's response to the IOM report will serve as a guide in developing these activities and identifying additional research priorities. The second TBESC meeting is scheduled for May 2002.

Some **ACET** members were extremely frustrated and disappointed with the confusing and poorly defined TBESC process. CDC did not clearly state during the application process that a signed contract was not a commitment of funds. The eight applicants who signed contracts and expected TBESC resources to be forthcoming were embarrassed after being informed of their "non-funded" status. This situation resulted from the program component of TBESC serving as the intermediary between applicants and CDC's Procurement and Grants Office (PGO). The lack of communication, misunderstanding and secondhand information have caused chaos in some states. For ACET members who were affected by the TBESC process and wished to express their concerns in writing, CDC committed to providing contact information for the appropriate PGO representatives.

***ACET Business*.** Several items raised during the meeting were clarified or brought to closure.

- TB in the southeast and the health disparity among U.S.-born blacks will serve as ACET's next project. DTBE will publish data on this issue in the *MMWR* or a peer-reviewed journal. A significant portion of the next meeting will be devoted to racial, cultural and social issues. Outside experts should be invited to provide guidance in these areas. Volunteers for the new "TB in Southeastern States Workgroup" will be solicited by e-mail, but the hope is that ACET representatives of southeastern states will serve.

- Dr. Castro has drafted a notice to readers on TST issues. The document will be distributed to ACET by e-mail and hopefully published in the *MMWR* before the next meeting. Dr. Blumberg will collaborate with DTBE and present the first status report of the TST Workgroup at the next meeting.

- The INS Workgroup will reconvene to revise the report based on ACET's comments during the meeting. A discussion of the updated document will be scheduled on the next agenda.

- CDC hopes to meet with APHL representatives before the next ACET meeting. In addition to a status report of this meeting, laboratory standards and the impact on the quality of TB treatment and services will be scheduled on the next agenda.

***Closing Session*.** In response to ACET's request, CDC confirmed that draft agendas would be distributed to members earlier. The next meeting is scheduled for February 6-7, 2002.

There being no further discussion, Dr. Nolan adjourned the ACET meeting at 11:58 a.m. on October 11, 2001.

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I hereby certify that to the best of my knowledge, the foregoing Minutes of the proceedings are accurate and complete.

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Date Charles M. Nolan, M.D., ACET Chair